

REMARKS

Applicants wish to thank the Examiner for the careful consideration given to this application. Currently, claims 33-39, 41, 46-62 and 64-77 are pending in this application. Claims 46, 51-52, 55, 56, 58-60, 64, 65, 68, 69, 71, 74 and 77 have been withdrawn, and claims 1-32, 40, 42-45 and 63 were previously cancelled. Applicant addresses each of the objections and rejections set forth in the Office Action, in the order presented therein.

35 U.S.C. § 103

The Examiner has rejected claims 33-39, 41, 53-54, 57, 61, 62, 66, 67, 70, 72, 73, 75 and 76 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Publication No. 2004/0096848 to Thruë et al. (hereinafter, "Thruë"), in view of U.S. Patent No. 5,801,156 to Robinson et al. (hereinafter, "Robinson") and U.S. Patent Publication No. 2004/0259247 to Tuschl et al. (hereinafter, "Tuschl"). The Examiner has also rejected claims 47-50 under 35 U.S.C. § 103(a) as being unpatentable over Thruë, in view of Robinson and Tuschl and further in view of Tuschl (Nature Biotechnology Vol. 20:446-448 2002) (hereinafter, "Tuschl-Nature") and Noonberg et al. (U.S. Patent No. 5,624,803) (hereinafter "Noonberg"). Applicants respectfully disagree.

The pending claims are not obvious because the Office has failed to make a proper *prima facie* obviousness rejection because the combination of the references does not yield the present invention, that is an siRNA targeted to SEQ ID NO: 223, and the cited references do not create a reasonable expectation of success because the prior art would not have led one of skill in the art to anticipate success of a siRNA molecule that is effective to inhibit expression of HIF-1 α in a subject, effective to inhibit angiogenesis in a subject, or effective to treat an angiogenic disease in a subject.

The Office alleges that Thruë discloses an antisense oligonucleotide that "targets within the recited SEQ ID NO: 223," and, therefore, the disclosure of Thruë's SEQ ID NO: 3, which only discloses a portion of SEQ ID NO: 223 has "shown that the target region defined by SEQ ID NO: 223 was known to be an accessible region for nucleic acid hybridization inhibitors." (Final Office Action, page 4). Applicants respectfully disagree with the Office's characterization of the Thruë reference because the Thruë reference has not shown that the target region defined by SEQ ID NO: 223 would have been obvious.

The Thru reference discloses SEQ ID NO: 3, which consists of *only* 16 nucleotides. SEQ ID NO: 223 of the present application, and included in all the independent claims, comprises 21 nucleotides. Contrary to the Office's assertions, a 16 nucleotide sequence does not define a target region that comprises 21 nucleotides. Thru's SEQ ID NO: 3 is missing almost a quarter (24%) of the nucleotides present in SEQ ID NO: 223. The Office has failed to put forward any evidence why one of skill in the art would have expanded SEQ ID NO: 3 to include all of the nucleotides present in the presently claimed target sequence, SEQ ID NO: 223. The Office, without support other than its own conclusion, stated that in view of Thru the region defined by SEQ ID NO: 223 "was known to be accessible." Thru has not shown that the region defined by SEQ ID NO: 223 was accessible. Thru has only disclosed the sequence disclosed in SEQ ID NO: 3 may be a target for antisense oligonucleotides.

The deficiency of the Thru reference is not cured by the other references cited by the Office. The other references are general references about siRNA and VEGF. Nothing in those references would have led one of skill in the art to modify SEQ ID NO: 3 to yield SEQ ID NO: 223 of the present invention. Therefore, the Office has not supported a *prima facie* case of obviousness because the combination cited by the Office fails to yield the present invention. The Office's fails to explain how the disclosure of a sequence that does not consist SEQ ID NO: 233 renders claims reciting SEQ ID NO: 223 obvious. The Office appears to rely upon the fact that Thru used antisense directed against SEQ ID NO: 3 to show that another distinct target sequence would also have been obvious, but the Office offers no explanation as to why SEQ ID NO: 3 would have been modified to produce the claimed invention. Applicants respectfully request that if the rejection is maintained that the Office explain why the disclosure of SEQ ID NO: 3 would have led to the target defined by SEQ ID NO: 223 when SEQ ID NO: 223 comprises 5 more nucleotides than SEQ ID NO: 3. Therefore, because the combination of the cited references does not yield the present invention the *prima facie* obviousness rejection has not been properly made.

Even if the Office had provided sufficient evidence to show that a person of ordinary skill in the art would modify the target from SEQ ID NO: 3 to SEQ ID NO: 223, which it has not, there is nothing in the references that would have led one of skill in the art to have a reasonable expectation of success that an siRNA targeted to SEQ ID NO: 223 would be effective in the claimed methods. As discussed above, SEQ ID NO: 3 does not define SEQ ID NO: 223 and the

Office has not presented sufficient evidence as to why a different target sequence would have been obvious. Ultimately, the Office appears to be alleging that it would have been “obvious to try” siRNA targeted to SEQ ID NO: 223 in the claimed methods because of a shorter sequence being disclosed. Obvious to try, however, is not analyzed in a vacuum. As the Supreme Court recently stated:

When there is a design need or market pressure to solve a problem and there are a *finite number* of identified, *predictable* solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the *anticipated success*, it is likely the product not of innovation but of ordinary skill and common sense.

KSR v. Teleflex, (82 USPQ2d 1385, 1390 (2007), emphasis added). Here, the Office has failed to show that there were a “finite number of identified, predictable solutions” that would have led one of skill in the art to anticipate success using an siRNA targeted to SEQ ID NO: 223. A similar attempt to invalidate a patent using “obvious to try” was also rejected by the Federal Circuit in *Takeda Chemical Indus. Ltd. v. Alphapharm Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007).

In *Takeda*, the defendant argued that the claimed compound was obvious because it would have been “obvious to try” to make and use the compound. *Id.* at 1176. The court held that the invention was not obvious under the obvious to try standard because

Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation.

Id. Here, like in *Takeda*, the prior art had not identified a predictable solution for an siRNA molecule targeted to SEQ ID NO: 223 that would be effective in the claimed methods. The Thru reference discloses SEQ ID NO: 3 but does not disclose SEQ ID NO: 223, a sequence that is longer and structurally different. Furthermore, the Thru reference shows through its own data that one of skill in the art cannot predict what target sequences will and will not work.

Thru demonstrates that the prior art did not identify a predictable solution because the Thru reference discloses that certain, but not all, antisense molecules targeting SEQ ID NO: 3 are effective. In the provisional that is the basis of the Thru published patent application (and the only material that is prior art against the present application), Thru tested eight (8) antisense oligonucleotides targeted to SEQ ID NO: 3 (See Table 2, p. 40 of U.S. Provisional 60/370,126). Of these 8 oligonucleotides that target to SEQ ID NO: 3, only 3 had any effect on HIF-1 α

expression. The differences in activity appear to be correlated with structural changes in the antisense oligonucleotides because the overall sequence is identical in each oligonucleotide. Therefore minor changes to the linkages and other structural components of the oligonucleotides targeting SEQ ID NO: 3 can have a major effect on the oligonucleotide's activity or effectiveness. One of skill in the art, therefore, would not have had a reasonable expectation of success using an siRNA molecule targeted to a different sequence (SEQ ID NO: 223) because, as demonstrated by Thru, not all of the antisense molecules tested worked, which indicates that structural variations can and do have a major impact on the effectiveness of an oligonucleotide.

In Thru, the oligonucleotide was a single-stranded antisense molecule where the linkages, for example, were modified. In the present application the molecule targeted to SEQ ID NO: 223 is an siRNA molecule, which is double-stranded and longer than SEQ ID NO: 3. Since structural difference appear to have a major impact on the oligonucleotide's effectiveness, there can be no reasonable expectation of success when the Thru oligonucleotide would have to not only be extended, but also then be made into a double-stranded molecule. The Office has failed to state why one of skill the art would have a reasonable expectation of success when modifying the Thru invention to produce the presently claimed invention involves substantial and major modifications when the minor changes disclosed in Thru can remove any activity of the antisense oligonucleotide. Therefore, Thru is evidence that the prior art did not provide "a finite number of identified, predictable solutions" because of the differences in activity within the same sequence itself, let alone a target that comprises additional oligonucleotide bases.

Additionally, there is nothing in the combination of the references that would lead one of skill in the art to have "anticipated success." There is no anticipated success because prior to the present invention there was no reasonable expectation that the claimed compositions targeted to SEQ ID NO: 223 would be effective in the claimed methods. As the M.P.E.P. states, "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." (M.P.E.P. § 2141). The Office has failed to put forward an articulated reason as to why there would have been a reasonable expectation of success that a siRNA molecule targeted to SEQ ID NO: 223 would be effective in the claimed methods. The Office generally points to facts that the gene and siRNA were known but cannot show any evidence that one of skill in the art would have expected an siRNA molecule targeted to SEQ ID NO: 223, and not

SEQ ID NO: 3, would be effective in the claimed methods. Without such an expectation the obviousness rejection cannot be maintained.

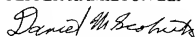
Accordingly, because the combination does not yield the present invention and one of skill in the art would not have had a reasonable expectation of success the pending claims are not obvious. In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

In light of the amendments and remarks presented herein, it is believed that the pending claims are in condition for allowance and notice to such effect is respectfully requested. The Commissioner is hereby authorized to charge Deposit Account No. 50-0436 for any additional fees that may be due in connection with this response. Should the Examiner have any questions regarding this application, the Examiner is invited to initiate a telephone conference with the undersigned.

Respectfully submitted,

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